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(54) Pharmaceutical and/or Cosmetic Composition and the Use Thereof

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Abstract

A pharmaceutical and/or cosmetic composition for topical use is described, wherein said composition comprises at least one active ingredient and a carrier for the penetration of the active ingredient into the skin. Said active ingredient is linoleic acid and/or at least one linoleic acid derivative.

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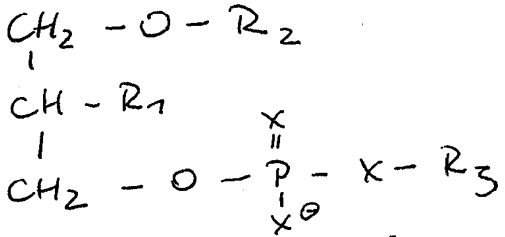
Pharmaceutical and/or cosmetic composition and the use thereof

This invention relates to a pharmaceutical and/or cosmetic composition with the characteristics of the generic part of claim 1 and the use of such a composition.

Pharmaceutical and/or cosmetic compositions for topical use are known since a long time.

Besides the conventional ointments, creams, lotions, emulsions or suspensions, which usually just act locally on the treated skin area, other systems are known comprising a carrier material, wherein the carrier material warrants the penetration of the active ingredient contained in the carrier material into the skin or through the skin barrier.
DE PS 38 29 899, published on March 3, 1990, describes pharmaceutical compositions of this kind, wherein the active ingredients are phospholipid derivatives of the following formula (I).



In the formula I R_1 stands for hydrogen, a lower aliphatic alkyl group with 1 to about 12 carbon atoms, an alkoxy group with about 6 to 30 carbon atoms, an alkylcarbonyloxy group with about 6 to 30 carbon atoms, a furanosyl or pyranosyl group with 4 to about 50 carbon atoms, and in total up to 10 glycosidically linked furanose and/or pyranose rings corresponding to the mono-, di-, and oligosaccharides, R_2 is an aliphatic alkyl group with about 6 to 30 carbon atoms or an aliphatic alkylcarbonyl group with about 6 to 30 carbon atoms, X stands for oxygen, sulfur or the imino group, and R_3 is the structure of an amino alcohol R_4-$N(R_5R_6)$ in which R_4 is an alkylene bridge group with 1 to about 12 carbon atoms optionally carrying a carboxyl group, and R_5 and

R_6 independently of one another stand for hydrogen or lower alkyl with 1 to 4 carbon atoms.

It is the object of the present invention to provide a novel pharmaceutical and/or cosmetic composition for topical use, which possesses a particularly high pharmaceutical and/or cosmetic efficacy.

This object is solved by a pharmaceutical and/or cosmetic preparation with the characteristic features of claim 1.

The inventive pharmaceutical and/or cosmetic composition which is to be applied topically, comprises like the aforementioned compositions according to the state of the art, at least a carrier and at least one active ingredient, wherein the carrier makes safe that the active ingredient does not remain locally on the skin surface but penetrates into the skin or through the skin barrier.

More specifically the inventive pharmaceutical and/or cosmetic composition comprises linoleic acid and/or at least one linoleic acid derivative as active ingredient.

The inventive pharmaceutical and/or cosmetic composition provides several advantages.

Firstly said composition possesses a particularly high pharmaceutical and/or cosmetic efficacy, especially in the treatment of skin disorders and preferably in the treatment of unclean or acnegenic skin, acne and accompanying disorders related with acne.

This is due to the fact, that the active ingredient contained in the inventive composition, i.e. linoleic acid and/or at least said one linoleic acid derivative, rapidly penetrates into the skin or through the skin barrier and therefore very soon after the application of the inventive composition high concentrations of the active ingredient are reached in the affected area.

The fact that the inventive composition is applied topically, i.e. through the skin, leads to a particularly low frequency in side effects caused by the inventive composition. This is in strong contrast to many known products which are administered by for instance the oral route or by injection.

It could surprisingly be shown, that the active ingredient linoleic acid and/or linoleic acid derivative contained in the inventive pharmaceutical and/or cosmetic composition possesses a high pharmaceutical and cosmetic efficacy, in particular when said composition is being used for the therapy and or prophylaxis of unclean or acnegenic skin, acne, pimples, pustules and/or other accompanying disorders related with acne.

In this respect it could be observed, that already after a few

topical treatments with the inventive composition an obvious improvement was observed. The number of pimples, follicles, pustules, efflorescences and comedones was reduced to such an extent that already after a few days of treatment with the inventive composition the skin became cleaner, softer and smoother.

Also in acne, especially in severe and long-lasting acneiform dermal disease, the treatment with the subject invention led to a marked improvement and in most cases to a permanent healing of the affected area. The treatment period necessary for such improvement and healing was relatively short. Depending on the grade of disorder in evident recovery and in the most cases a permanent healing was noticed within a treatment period between 2 weeks and nearly 6 weeks, which cannot be achieved by conventional acne drugs.

Beyond this healing effect, the composition according to the invention, gave the treated skin area a markedly smoother and more elastic character, which gave the patients the impression of a healthy skin.

In a first embodiment of the composition according to the invention, the composition comprises liposomes as carrier. With liposomes pursuant to the invention, unilamellar, oligolamellar and multilamellar vesicles and fusioned bodies are being meant, their formation being dependent upon the respective preparation procedure. Said liposomes possess an empty inner space surrounded by a membrane. Their diameter varies between 15 and 3500 nm, especially between 100 nm and 300 nm.

In the same manner as biological cells, liposomes can store in their vesicular inner space water-soluble compounds and/or lipophilic substances in their membranes. In this respect, in the subject invention the linoleic acid or the linoleic acid derivative are, due to their lipophilicity, stored in the liposomal membranes.

As liposome-forming compounds synthetic or natural polymers may be used, like e.g. polyacrylates, polyesters, and/or polymeric cellulose-derivatives.

In a preferred embodiment of the inventive composition the liposomes are formed from at least one phospholipid. Such phospholipids, which are preferably a mixture of phospholipids, can be derived from natural sources like plant and animal lecithins, from which by extraction and subsequent purification according to known procedures such phospholipids forming the liposomes may be obtained.

Preferably said phospholipids and said phospholipid mixtures are isolated from eggs, oil seeds and oil fruits, like e.g. coconut,

copra, palm kernels, groundnut, rape, sun flower, oil palms and/or olives, and as mentioned before after the required purification and concentration processed to liposomes.

In an especially preferred embodiment of the inventive composition the liposomes are formed from at least one phospholipid or a phospholipid mixture which has been isolated according to known processes from a plant source, especially sunflower or soybean. In this respect, such liposomes represent vesicles as described above, the membrane of which consists of phospholipids of plant origin, especially sunflower or soybean.

The composition according to the invention displays especially in the case, when it comprises liposomes which are formed from soybean phospholipids containing between 70 and 100 % by weight 1,2-diacylglycero-3-phosphocholine [(3-sn-phosphatidyl)choline, soybean] an excellent pharmaceutical and/or cosmetic efficacy. This is due to the fact that said liposomes, rich in 1,2-diacylglycero-3-phosphocholine and therefore reproducibly formed, have a large storage capacity for linoleic acid and/or linoleic acid derivatives, and may therefore be loaded with linoleic acid and/or the linoleic acid derivative in a reproducible manner. This then warrants that on applying identical amounts of the inventive composition on the skin, always identical amounts of linoleic acid and/or linoleic acid derivative are applied and through such a transport carrier are transferred into the skin or through the skin barrier, which again guarantees the reproducibility of the healing rate obtained with the composition according to the subject invention. Therefore such an embodiment of the inventive composition is especially preferred when the composition according to the invention is being used for the pharmaceutical or cosmetic treatment of unclean or acnegenic skin, pimples, comedones, efflorescences, pustules, wheales as well as acne and accompanying disorders related with acne.

The proportion of the carrier contained in the subject composition must be sufficiently high to warrant the free transport of the composition into the skin or through the skin barrier. Preferably said composition comprises between 5 and 50 % by weight and especially between 15 and 30 % by weight carrier and preferentially the above-mentioned phospholipid type carrier, based on the overall composition.

In order to facilitate at the topical application the uptake of the subject composition through the skin, the subject composition possesses a fluid or semi-solid consistency, and is preferably formulated as a gel or as a fluid. Such a gel type or fluid formulation can be obtained, when the inventive composition comprises, besides the carrier and the active ingredient (linoleic acid and/or a linoleic acid derivative), water and/or a non-toxic solvent, especially a water-soluble alcohol. Especially suited as a water-soluble alcohol are ethanol, 1-propanol and 2-propanol and/or propylene glycol. Instead of water all aqueous systems may be used according to the subject invention, like e.g. purified water, distilled water, de-ionised water and aqueous

salt solutions, preferably physiological sodium chloride solutions or buffer solutions, preferably phosphate buffers.

In the previous paragraphs it has been shown, that the inventive composition comprises linoleic acid and/or at least one linoleic acid derivative. In this respect there are several basic possibilities to provide the inventive composition with linoleic acid or the at least said one linoleic acid derivative.

The first possibility is, that the active ingredient (linoleic acid and/or the linoleic acid derivative) is physically incorporated into the carrier. When for instance the above described liposomes are used, and especially the phospholipid liposomes, then the active ingredient is preferentially entrapped in the membrane or in the phospholipid membrane respectively, which surrounds the ball-like vesicles as an outer envelope. In addition to this or instead of such an entrapment, there is the further possibility that the active ingredient is contained in the form of an aqueous dispersion inside the vesicles.

Instead of the aforementioned physical incorporation of linoleic acid or the at least one linoleic acid derivative into the carrier, the active ingredient (linoleic acid and/or the at least one linoleic acid derivative) may, according to a second possibility, be chemically incorporated into the carrier.

A third possibility of the inventive composition combines the aforementioned first and second possibility, meaning that according to this possibility the linoleic acid and/or the linoleic acid derivative is incorporated physically and chemically at the same time.

A further development of such a third possibility uses as carrier a phospholipid. The linoleic acid and/or the at least one linoleic acid derivative according to such a suitable embodiment of the inventive composition being bound chemically and physically to the phospholipid. Such a chemical bonding of the linoleic acid and/or the linoleic acid derivative can be reached by the acylation of the phospholipid carrier with the linoleic acid and/or the linoleic acid derivative. Such an embodiment excels by a particularly high pharmaceutical and/or cosmetic efficacy.

It goes without saying, that such embodiments of the inventive composition may be used, which comprise a phospholipid acylated with linoleic acid and/or a linoleic acid derivative as active ingredient, such an embodiment then comprising the active ingredient (linoleic acid and/or the linoleic acid derivative), taken from the viewpoint of the above three possibilities, only in chemically-bound form.

In the preceding text passages it has been described, that the carrier comprises a phospholipid or a phospholipid mixture. As already mentioned, suitable material for such a carrier are especially lecithins of plant and/or animal origin. The inventive

composition comprises especially 1,2-diacylglycero-3-phosphocholine (3-sn-phosphatidylcholine) alone or in a mixture with further phospholipids. Such further phospholipids which may be present in the inventive composition as carrier, are preferably 1,2-diacylglycero-3-phosphoethanolamine, 1,2-diacylglycero-3-phosphoinositol, 1,2-diacylglycero-3-phosphoserine, 1,2-diacylglycero-3-phosphoglycerol and 1,2-diacylglycero-3-phosphate, all of them alone or together with others.

In case the inventive composition comprises the aforementioned phospholipid acylated with linoleic acid and/or the linoleic acid derivative, then there is a possible differentiation between the acylation with the linoleic acid and/or the linoleic acid derivative in the 1-position of the phospholipid, the acylation with the linoleic acid and/or the linoleic acid derivative in the 1- and the 2-position and the acylation with the linoleic acid and/or the linoleic acid derivative in the 2position. Accordingly the subject composition comprises 1linoleoyl-3-phosphates, 1,2-dilinoleoyl-3-phosphates and/or 2linoleoyl-3-phosphates of the previous art.

An especially suitable embodiment of the inventive composition comprises at least one phospholipid or phospholipid mixture acylated with linoleic acid and/or a linoleic acid derivative of the above kind, in which at least 60 % by weight of the acyl groups are linoleic acid and/or linoleic acid derivative.

In an especially suitable and highly efficacious example of the above described embodiment of the inventive composition, the composition comprises a phospholipid mixture which is characterised by the following ratio of the acyl groups:

61-73 % by weight of the linoleic acid group,
10-14 % by weight of the palmitic acid group,
8-12 % by weight of the oleic acid group,
4-6 % by weight of the linolenic acid group,
3-5 % by weight of the stearic acid group and maximally
2 % by weight of other fatty acid groups.

For the treatment of acne and acneiform dermal disease, in particular such examples of the previous advantageous embodiment are suited, which comprise 15 to 30 % (based on the overall preparation) of a phospholipid mixture, which contains 70 to 100 % (based on the phospholipid mixture) of 1,2diacylglycero-3-phosphocholine. The acyl groups contained in said phospholipid mixture are at least 60 % linoleic acid (linoleoyl-rest). The rest of the acyl groups in the phospholipid mixture (maximally 40 % of the total amount) contains in particular the palmitic acid group, the oleic acid group, the linolenic acid group and/or the stearic acid group, preferably according to the mass ratio as indicated before.

As it has been mentioned in one of the previous passages, the inventive composition may contain for the phospholipid a

phospholipid mixture. Further phospholipids may be chosen from the group existing of 1,2-diacylglycero-3-phosphate, 1,2-diacylglycero-3-phosphoethanolamine, 1,2-diacylglycero-3-phosphoserine, 1,2-diacylglycero-3-phosphoinositol and/or 1,2-diacylglycero-3-phosphoglycerol. According to a preferred embodiment the phospholipid mixture comprises up to 30 % of these 1,2-diacylglycerophosphate types, the further 70 % of the phospholipid mixture being 1,2-diacylglycero-3-phosphocholine. The percentage rates in this paragraph are based on the total mass of the phospholipid mixture in the subject composition. As it has been noted before, the overall composition contains a share of 5 to 50 % of said phospholipid mixture as carrier material.

According to another, likewise preferred embodiment, the inventive composition contains for the phospholipid a 1,2-diacylglycero-3-phosphocholine, wherein the 1-acyl group is composed of a mixture of

45-61 % by weight linoleic acid groups,
19-26 % by weight palmitic acid groups,
8-12 % by weight of oleic acid groups,
4-6 % by weight of linolenic acid groups,
6-9 % by weight stearic acid groups and/or
2 % by weight other fatty acid groups.

In order to guarantee, that such a preparation contains the required amount of linoleic acid and/or the linoleic acid derivative, it is possible to add a certain amount of linoleic acid or the linoleic acid derivative, or according to a second possibility the 2-position is taken by another linoleic acid group. Most suitable are such 1,2-diacylglycero-3-phosphocholines, in which the 1-acyl group is composed of a mixture as indicated above and in which the 2-acyl group being composed of a mixture of

77-85 % by weight linoleic acid groups,
1-2 % by weight palmitic acid groups,
8-12 % by weight oleic acid groups,
4-6 % by weight linolenic acid groups,
0-1 % by weight stearic acid groups and/or
2 % by weight other fatty acid groups.

The concentration of linoleic acid and/or the at least one linoleic acid derivative, which is contained in the inventive composition as active ingredient bound by the carrier material in chemically or physically form, may vary between 1 and 30 % by weight, preferably between 3 and 18 % by weight. If the inventive composition is used as a cosmetic preparation, such a preparation contains linoleic acid and/or the linoleic acid derivative in concentrations which vary between 1 and 8 % by weight, whereas on the other hand respective pharmaceutical preparations contain concentrations of active ingredient which vary more specifically between 15 and 30% by weight. Such percentage values for the concentration of linoleic acid or the at least one

linoleic acid derivative are based on the overall preparation.

The composition pursuant to the invention possesses, as it was stated before, preferentially a gel type or fluid consistency. This means, that the inventive composition can be formulated into preparations such as gels, solutions, lotions, ointments, creams, sprays and/or aerosols. Conventional auxiliary materials such as thickeners (CMC, Gabopol, alginates, xanthan) and dermatological preservatives can be added. However, substances that stimulate fat production, cover or even lubricate the skin should be avoided. Furthermore, the preservative itself shall not penetrate. Preferred preservatives to be added are water-soluble alcohols, especially propylene glycol.

A particularly suitable embodiment of the inventive composition has proved to be a liposomal gel that contains

between 30 and 93 % by weight water,
between 0 and 20 % by weight of the solvent as said above,
between 1 and 30 % by weight linoleic acid and/or the at least one linoleic acid derivative, and
between 5 and 50 % by weight carrier, in particular the aforementioned phospoholipids.

Such a gel type preparation contains preferably the already mentioned alcohols as solvent, and has as a further advantage that it is particularly simple to use.

A typical fluid liposomal form of administration pursuant to the invention contains

between 69 and 94 % by weight water,
between 0 and 20 % by weight solvent,
between 1 and 30 % by weight linoleic acid and/or the at least one linoleic acid derivative, and
between 5 and 30 % by weight carrier, in particular the phospholipids as mentioned before.

In order to secure for the above fluid administration form pursuant to the invention a long storability, it is advisable to add a solvent to the preparation, in particular one or more of the aforementioned alcohols. Only when such patients are to be treated who show irritative skin reactions to solvents and in particular to water-soluble alcohols, it is recommendable to use the formulations which contain only water as fluid. The number of such sensitive patients is however relatively small.

To guarantee the required sterility in such fluid formulations pursuant to the invention which do not contain any organic solvent and in particular no alcohols, such fluid formulations are, according to a further embodiment, filled into air-tight ampoules. The volume contained in such ampoules is sufficient for a single application of the preparation.

A further method of realization of the preparation according to the invention, that is also preferred, involves a preparation comprising a first component and a second component which is packaged separatly from it. In other words this form of realization of the preparation according to the invention is composed of two components stored separately from each other whereby these two components are mixed with each other by the user immediately before the preparation according to the invention is employed. Hereby the first component contains a solvent, at least one electrolyte and/or water, whereby the solvent is chosen from the aforementioned solvents. Every electrolyte used in the medical field can be used as electrolyte, however the electrolyte is preferably a physiological saline solution. In this form of realization of the method according to the invention, the second component, which, as has already been stated, is packaged separately from the first component, contains the carrier material, the linoleic acid and/or the linoleic acid derivative and a solvent of the aforementioned type, if required. The addition of the solvent to the second component brings the advantage that this adaptation of the preparation according to the invention then takes the form of two liquid components that are then very readily mixed with each other immediately before use.

In order to adjust the necessary pH of the aforementioned advantageous realization form of the preparation according to the invention involving two components a further develepment of this realization form involves addition of a suitable pH regulator to one of the two components particularly the first component. Whereby the regulator used is preferably an aqueous buffer system or an appropriate base, whereby the pH of the mixed preparation ready for use lies between 5.5 and 8, preferably between 6.5 and 7.5.

With respect to the concentrations of the aformentioned particularly suitable form of the preparation according to the invention in which the first and second components are mixed immediately before application it should be said that the concentrations in the first components are between

50 % by weight and 80 % by weight water and

between 0 % by weight and 20 % by weight solvent

and in the second component they are between

3 % by weight and 15 % by weight of the phospholipid carrier material acylated with linoleic acid or at least one linoleic acid derivative and

0 % by weight to 15 % by weight solvent.

A further development of this aformentioned realization form involves the complete or partial replacement of the water (50 % by weight to 80 % by weight) contained in the first component by

an aqueous electrolyte solution and preferably by an aqueous physiological sodium chloride solution (0.5 % by weight to 2.5 % by weight sodium chloride). Further development containing electrolyte is characterized by high sterility and a particularly long storage life.

Furthermore, the first component and/or the second component can also contain normal additives, such as, for example, pH regulators, buffer systems, emulsifiers and/or thickening agents.

As it has already been stated repeatedly, the subject composition is in particular used for the prophylaxis and/or therapy of acne and/or acneiform dermal disease. It was a surprising observation, that the composition according to the invention when used in acne or in acneiform dermal disease rapidly led to a complete healing of such disorders, without any unpleasant or disturbing side effects to be observed.

Acne in the context of this invention means all dermal disorders, in which comedones, papules, pustules or efflorescences develop, in particular disorders like Acne catchecticorum, Acne necroticans, Acne varioliformis, Acne picea, Acne vulgaris, Acne conglobata and Acne juvenilis.

The composition according to the invention can comprise in addition conventional drugs for topical application, like e.g. erythromycin, the salts of erythromycin or its derivatives, tetracycline hydrochloride and/or retinoic acid (Tretinoin USP XXI).

Suitable ratios of these conventional therapeutic agents are

for erythromycin 0,5 –4 % by weight,
for tetracycline 1–5 % by weight,
for azelaic acid 5–20 % by weight, and
for tretinoin 0,025 to 0,1 % by weight.

According to a further embodiment of the composition according to the invention, the different ingredients of the composition are packed separately. This can be achieved by mixing, directly prior to use a first dry component, which contains the carrier and the active ingredient, with a second component which consists of the solvent as described above and/or water. The preparation of the dry component may be achieved by pulverisation, granulation, lyophilisation or any other appropriate known technology of the combination of active ingredient and carrier.

It is evident that the dry component according to the description in the previous paragraph can contain additionally any of the previously listed therapeutic agents.

Suitable forms of administration are indicated in the subclaims.

The following examples further illustrate the invention.

For the preparation of the compositions according to the following examples 1 to 6 different soybean phospholipids were used. On the one hand a soybean phospholipid A was used containing as main component 76 ± 3 % by weight phosphatidylcholine and a further 3 ± 3 % by weight lysophosphatidylcholine, on the other hand a soybean phospholipid B was used, which contained the main component phosphatidylcholine in an amount of 93 ± 3 % by weight and again 3 ± 3 % by weight of lysophosphatidylcholine.

Example 1

Soybean phospholipid A (330 kg) containing 100 kg linoleic acid was taken up in a solvent mixture, consisting of 729 l purified water and 257 l ethanol.
After homogenisation in vacuum at 300 mbar, the pH value of the gel formed was adjusted to 6,5 ± 1,5 by addition of sodium hydroxide.

The transparent gel which was formed had a total content of free and bound linoleic acid of 8,05 % by weight. The viscosity of the gel was 5000 ± 3000 mPa.s.

The gel suited the purity requirements of the Category 2 of the DAB 10 for final products.

Under appropriate storage conditions, meaning storage in airfree environment and at 25 °C, the gel was storable for at least 24 months.

Example 2

In a mixture of solvents, consisting of 12,793 g purified water and 3,2000 g propylene glycol, an amount of 4 kg soybean phospholipid B, containing 1,4 kg bound linoleic acid, was added. After homogenisation a slightly transparent, soft gel appeared, with a total content of free and bound linoleic acid of 7 % by weight and a pH value of 6,5 ± 1,5, this pH value being adjusted by the addition of the necessary amount of sodium hydroxide. The viscosity of the gel amounted to 3000 to 7000 mPa.s.

Example 3

A dispersion of 45 kg soybean phospholipid A containing 15,7 kg linoleic acid in 400 l purified water was prepared. This dispersion was stirred to homogeneity. After filtration the dispersion was filled into ampoules.

This dispersion had a total content of free and bound linoleic acid of approximately. 3,5 % and a pH value of 6 ± 1, which was based on the addition of a required amount of sodium hydroxide to the dispersion.

The dispersion prepared according to this description was stable

for at least 24 months.

Example 4

In a mixture of solvents, consisting of 401,4 kg purified water and 85 kg ethanol, an amount of 50 kg phospholipid B containing 17,5 kg linoleic acid was dispersed. A turbid dispersion was obtained in this manner, with a pH value of 6 ± 1, this pH value being adjusted by the addition of sodium hydroxide.

The total content of free and bound linoleic acid was 3,5 % by weight.

Example 5

In a mixture of solvents, consisting of 401,4 kg purified water and 85 kg 2-propanol, an amount of 50 kg phospholipid B containing 17,5 kg linoleic acid was dispersed. A turbid dispersion was obtained in this manner, with a pH value of 6 ± 1, this pH value being adjusted by the addition of sodium hydroxide.

The total content of free and bound linoleic acid was 3,5 % by weight.

Example 6

In a mixture of solvents, consisting of 12,793 g purified water and 3,2000 g propylene glycol, an amount of 4 kg soybean phospholipid B, containing 1,4 kg bound linoleic acid and addtitional an additive of 400 g free linoleic acid, was added. After homogenisation a slightly transparent, soft gel appeared, with a total content of free and bound linoleic acid of 9 % by weight and a pH value of 6,5 ± 1,5, this pH value being adjusted by the addition of the necessary amount of sodium hydroxide. The viscosity of the gel amounted to 3000 to 7000 mPa.s.

To test the efficacy of the pharmaceutical compositions pursuant to the invention, the preparations of Examples 3 and 6 were investigated in 13 juvenile subjects. Besides their affected skin which was characterised by the presence of pimples, comedones and efflorescences, the subjects were in healthy condition.

The subjects were treated daily during a 8 week treatment period with the preparation. The content of an ampoule containing 5 ml of composition according to Example 3 or 6 was applied by the subjects themselves on the left side of the face and lightly rubbed in. As many of the preparation was applied, as could be taken up by the skin. The right side of the face was left untreated by all subjects during the whole treatment period.

Other active cosmetic or pharmaceutical treatment was not allowed during the test period.

At the beginning of the treatment, and 2,4 6 and 8 weeks after

the beginning of the treatment the condition of the skin was evaluated. For this test the treated and non treated parts of the face were covered with a foil and a physician has marked the comedomes and the efflorescences upon the foil (projection slide).

The following table indicates the mean values for the number of comedones and efflorescences.

Table 1

Results of the treatment with the preparation produced according to example 3.

Number of comedones

	duration of treatment in weeks				
part of the face	0	2	4	6	8
left side	18,0	11,2	5,6	4,9	2,2
right side	18,9	16,8	15,7	16,1	13,8

Number of efflorescences

	duration of treatment in weeks				
part of the face	0	2	4	6	8
left side	15,2	7,1	3,2	2,4	1,1
right side	15,4	14,7	13,5	13,5	13,2

Table 2

Results of the treatment with the preparation produced according to Example 6.

number of comedones

	duration of treatment in weeks				
part of the face	0	2	4	6	8

left side	19,0	12,2	5,9	4,2	1,2
right side	19,9	17,2	16,3	16,8	15,8

number of the efflorescences

	duration of treatment in weeks				
part of the face	0	2	4	6	8
left side	15,7	6,3	2,2	1,8	1,0
right side	17,4	16,7	14,9	15,2	15,3

In none of the treated subjects any sign of adverse effects or the occurrence of skin irritation could be observed.

Example 7

A mixture was prepared from 10 % by weight soybean phospholipids containing

80 % by weight 1,2-diacylglycero-3-phosphocholine,

8 % by weight 1,2-diacylglycero-3-phosphate,
4 % by weight 1,2-diacylglycero-3-phosphoethanolamine and
8 % by weight unspecified other phospholipids and

90 % by weight of a physiological saline solution (1 % by weight sodium chloride in water).

The total acylgroup ratio of the phospholipids was

61-73 % by weight linoleic acid groups,
10-14 % by weight palmitic acid groups,
8-12 % by weight oleic acid groups,
4-6 % by weight linolenic acid groups,
3-5 % by weight stearic acid groups and
2 % by weight other fatty acid groups.

The product was a liposomal dispersion which was produced in sterile form and contained therefore no preservatives at all. The liposomal dispersion could be filtered and could be applied directly on the skin.

Example 8

A gel was made using the phospholipids described in example 7. The gel contained 20 % by weight of the phospholipid according to example 7, 16 % by weight ethanol and 64 % by weight water.

The product was a liposomal composition that could be applied directly on the skin.

In each of the following examples 9 to 25 the phospholipid mixture described in example 7 was used.

Example 9

A solution was made, containing

2 % by weight erythromycin,
16 % by weight phospholipid and
82 % by weight propylene glycol.

The solution could be applied directly on the skin.

Example 10

A solution was made, containing

2 % by weight erythromycin,
29 % by weight phospholipid,
16 % by weight ethanol and
62 % by weight propylene glycol.

This solution could be applied directly on the skin as well.

Example 11

An ointment was made, containing

2 % by weight erythromycin,
12 % by weight phospholipid and
86 % by weight cetylstearylalcohol.

Example 12

An ointment was made, containing

2,5 % by weight erythromycin,
18 % by weight phospholipids,
20 % by weight propylene glycol and
59,5 % by weight cetylstearylalcohol.

Example 13

A gel was made, containing

4 % by weight erythromycin,
20 % by weight phospholipid,
16 % by weight ethanol and
60 % by weight water.

Example 14

A liposomal dispersion was made, containing

1 % by weight erythromycin,
10 % by weight phospholipid,
16 % by weight ethanol and
73 % by weight water.

Erythromycin was placed in a flask and dissolved by shaking with the solvent (ethanol, water) containing the phospholipids. A ready-made liposomal dispersion was formed which is to be prepared just before its first use. It is intended for prompt use and should be stored cold.

Example 15

A ready-made liposomal dispersion was prepared as described in Example 14, containing

1,2 % by weight erythromycin,
10 % by weight phospholipid,
20 % by weight propylene glycol and
68 % by weight water.

This liposomal dispersion had to be prepared directly before its first use and was intended for prompt use.

Example 16

Two systems were separately prepared, which had to be combined directly prior to the first use.

The first system contained

1,2 % by weight erythromycin and

20 % by weight ethanol,

whereas, the second system contained

5 % by weight phospholipid,
16 % by weight propylene glycol and
57,8 % by weight water.

Solutions 1 and 2 were combined just before the first use. A ready-made liposomal dispersion was formed, which was intended for prompt use.

Example 17

An ointment was made, containing

3 % by weight tetracycline hydrochloride,
16 % by weight propylene glycol and
57,8 % by weight water.

Example 18

An ointment was made, containing

2,5 % by weight tetracyclinehydrochloride,
22,5 % by weight phospholipid,
25 % by weight anhydrous lanolin,
10 % by weight propylene glycol and
40 % by weight vaseline.

Example 19

A gel was made, containing

5 % by weight acelaic acid,
20 % by weight phospholipid,
16 % by weight propylene glycol and
59 % by weight water.

Example 20

A gel was made, containing

15 % by weight acelaic acid,
20 % by weight phospholipid,
16 % by weight ethanol and
49 % by weight water.

Example 21

A cream was made, containing

10 % by weight azelaic acid,
20 % by weight phospholipid,

16 % by weight propylene glycol,
12 % by weight mono-, diglycerides and
42 % by weight water.

Example 22

A gel was made, containing
0,025 % by weight tretinoin,
20 % by weight phospholipid,
16 % by weight ethanol and
63,975 % by weight water.

Example 23

A gel was made, containing

0,05 % by weight tretinoin,
10 % by weight phospholipid,
16,7 % by weight ethanol,
2,2 % by weight xanthan and
71 % by weight water.

Example 24

A solution was made, containing

0,5 % by weight tretinoin,
10 % by weight phospholipid,
24 % by weight Macrocol 400,
17,95 % by weight ethanol and
48 % by weight propylene glycol.

Example 25

A cream was made, containing

0,05 % by weight tretinoin,
16 % by weight phospholipid,
24 % by weight cetylstearylalcohol,
22 % by weight propylene glycol and
37,95 % by weight water.

To test the efficacy of the compositions described above, a third investigation on test persons was performed, in which the liposomal dispersion of Example 7 was applied to the affected test areas of 14 subjects twice daily for eight weeks.

The interpretation was done by marking the comedones and the efflorescences on a projection slide, as was described for the previous investigation.

Skin surface lipids were sampled by direct contact of the skin

with a mixture of n-hexane/isopropanol (3:2). The total linoleic acid content of these samples was determined by gas chromatography after conversion into the methyl ester.

The test results are given in table 3. The averages from 14 subjects are shown in figure 1 for the number of comedones and efflorescences as well as the linoleic acid content of the skin as function of the time of treatment. It is clear from the graphic representation in figure 1 that the number of comedones and efflorescences has declined by an average of about 50 % of the initial value after only two weeks of treatment. After treatment with the composition according to Example 7 for eight weeks, an evidently further reduction occurred in the number of comedones and efflorescences, associated with an increase of the linoleic acid content of the skin surface.

In figure 2 the efficacy of various conventional acne agents is shown, in the form of the percentage decline in the number of comedones after 2 months.

Comparison of figures 1 and 2 shows clearly, that the treatment with the liposomal dispersion according to Example 7 was even more effective than isotretinoin, the most powerful acne agent up to now. In contrast to isotretinoin, however, no side effects have been observed in the studies up to now.

Example 26

A composition was prepared using the soja phospholipid A mentioned at the start, whereby the composition was characterized by a first component packed in vessel 1 and a second component packed in vessel 2.

The contents of vessel 1 were characterized by the following components:

demineralized water	73.83 g
ethanol DAB 9	10 g
10 % sodium hydroxide	0.17 g.

Vessel 2 had the following contents:

phospholipid A	10 g
ethanol DAB 9	6 g

Example 27

A composition was also divided between 2 vessels. Whereby vessel 1 contained

demineralized water	73.83 g
isopropyl alcohol	10 g
10% sodium hydroxide	0.17 g

and vessel 2 had the following contents:

phospholipid A	10 g
isopropyl alcohol	6 g.

Example 28

A further composition was prepared with vessel 1 containing

1% physiological saline solution	73.83 g
ethanol DAB 9	10 g
10% sodium hydroxide	0.17 g

and vessel 2 containing

phospholipid A	10 g
ethanol DAB 9	6 g

Example 29

As in the aforementioned examples 26 to 28 a composition prepared consisting of 2 components, whereby vessel 1 contained

1% physiological saline solution	73.83 g
isopropyl alcohol	10 g
10 % sodium hydroxide	0.17 g

Vessel 1 had the following contents:

phospholipid A	10 g
isopropyl alcohol	6 g

The components previously prepared in separate vessels in examples 26 to 29 were mixed together by brief shaking (30 seconds). This led to the formation from the components of example 26 of a brownish liposomal gel with a mean liposome diameter of 380 nm and a pH of 6.8, the components of example 27 also yielded a brownish, liposomal gel with a mean particle size of 311 nm and a pH of 7.0, the components of example 28 yielded a milky liposomal fluid with a mean particle size of 540 nm and a pH of 6.6, and the components of example 29 yielded a yellowish fluid liposomal preparation with a mean liposome particle size of 281 nm and a pH of 6.8.

table 1

Subject No.	Initially			after 2 weeks			after 4 weeks			after 8 weeks		
	C.	Ef.	L.S.	C.	Ef.	L.S.	C.	Ef.	L.S.	C.	Ef.	L.S.
1	28	19	0,64	23	8	1,62	16	7	3,49	12	6	3,57
2	32	4	0,34	15	2	1,45	11	2	1,94	11	0	2,97
3	6	10	0,40	4	4	4,45	1	7	1,21	0	5	2,90
4	38	27	0,57	23	6	0,54	7	13	3,33	7	0	3,24
5	16	15	1,40	16	3	1,90	18	0	2,63	14	0	3,47
6	0	33	1,30	0	19	2,13	0	11	2,80	0	3	3,40
7	35	25	1,94	22	7	3,22	19	1	6,28	17	0	4,59
8	0	12	0,86	0	8	4,04	0	9	4,00	0	6	3,82
9	34	4	2,07	10	2	2,93	12	0	3,49	12	0	3,28
10	34	15	1,12	16	3	3,37	13	2	4,83	6	0	4,62
11	30	29	1,70	17	25	2,27	18	23	2,25	13	8	3,10
12	28	15	1,77	16	2	1,96	11	3	2,12	4	4	3,24
13	2	9	1,70	0	4	2,03	0	7	2,40	3	5	2,92
14	9	8	0,57	6	0	1,20	4	0	1,79	0	0	3,14

C. = comedones

Ef.= efflorescence

L.S.= % linoleic acid in the eluate based on total fally acid content.

Patent Claims

1. A pharmaceutical and/or cosmetic composition for topical use, comprising at least one active ingredient and a carrier for the penetration of the active ingredient into the skin, wherein said active ingredient is linoleic acid and/or at least one linoleic acid derivative.

2. The composition according to claim 1, wherein said composition contains liposomes as carrier.

3. The composition according to claim 2, wherein said liposomes are constituted of at least one phospholipid.

4. The composition according to claim 3, wherein said phospholipid is a mixture of phospholipids.

5. The composition according to claim 3 or 4, wherein said phospholipid is of plant origin, especially a sunflower phospholipid or a soybean phospholipid.

6. The composition according to one of the preceding claims, wherein said composition contains 5 to 50% by weight, preferably 15 to 30% by weight, of the overall said composition of said carrier, which is preferably a phospholipid type carrier.

7. The composition according to claim 5 or 6, wherein said phospholipid of plant origin contains between 70 and 100 % by weight 1,2-diacylglycero-3-phosphocholine.

8. The composition according to one of the preceding claims, wherein said composition contains a water-soluble alcohol and/or water.

9. The composition according to one of the preceding claim, wherein said composition comprises linoleic acid and/or at least one linoleic acid derivative, which is chemically and/or physically incorporated into the carrier.

10. The composition according to claim 1 to 8, wherein said composition comprises linoleic acid and/or a linoleic acid derivative, which is chemically incorporated into the carrier.

11. The composition according to one of the preceding claims, wherein said composition comprises besides linoleic acid and/or the at least one linoleic acid derivative further a phospholipid acylated with linoleic acid and/or the linoleic acid derivative.

12. The composition according to claim 10, wherein said composition comprises as active ingredient a phospholipid acylated with linoleic acid and/or the linoleic acid derivative.

13. The composition according to claim 11 or 12, wherein said phospholipid acylated with linoleic acid or the linoleic acid derivative is a 1,2-diacylglycero-3-phosphocholine.

14. The composition according to one of the claims 10 to 13, wherein said composition comprises a phospholipid acylated with linoleic acid or a linoleic acid derivative, whereby at least 60 % by weight of the acyl groups being linoleic acid and/or a linoleic acid derivative.

15. The composition according to claim 14, wherein said composition comprises a phospholipid mixture acylated with linoleic acid or a linoleic acid derivative.

16. The composition according to claim 15, wherein said composition comprises a phospholipid mixture with a total acyl group ratio by weight of

61-73 % linoleic acid groups,
10-14 % palmitic acid groups,
8-12 % oleic acid groups,
4-6 % linolenic acid groups,
3-5 % stearic acid groups and/or
2 % other fatty acid groups.

17. The composition according to claim 15 or 16, wherein the phospholipid mixture comprises one or more other 1,2-diacylglycero-3-phosphates selected from the group consisting of

1,2-diacylglycero-3-phosphoethanolamine,

1,2-diacylglycero-3-phosphoinositol,

1,2-diacylglycero-3-phosphoserine,

1,2-diacylglycero-3-phosphoglycerol and

1,2-diacylglycero-3-phosphate.

18. The composition according to one of the preceding claims, wherein in said 1,2-diacylglycero-3-phosphocholine the 1-acyl group contains

45-61 % by weight linoleic acid groups,
19-26 % by weight palmitic acid groups,
8-12 % by weight oleic acid groups,
4-6 % by weight linolenic acid groups,
6-9 % by weight stearic acid groups and/or
2 % by weight other fatty acid groups.

19. The composition according to one of the preceding claims, wherein in said 1,2-diacylglycero-3-phosphocholine the 2-acyl group contains

77-85 % by weight linoleic acid groups,
1-2 % by weight palmitic acid groups,
8-12 % by weight oleic acid groups,
4-6 % by weight linolenic acid groups,
0-1 % by weight stearic acid groups and/or
2 % by weight other fatty acid groups.

20. The composition according to one of preceding claims, wherein said composition comprises between 1 and 30 % by weight, preferably between 3 and 18 % by weight, linoleic acid and/or linoleic acid derivative.

21. The composition according to one of the preceding claims, wherein said composition is a gel and comprises

between 30 and 93 % by weight water,
between 0 and 20 % by weight solvent,
between 1 and 30 % by weight linoleic acid and/or linoleic acid derivative and
between 5 and 50 % by weight phospholipid.

22. The composition according to one of the claims 1 to 21, wherein said composition is a fluid and comprises

between 69 and 94 % by weight water,
between 0 and 20 % by weight solvent,
between 1 and 30 % by weight linoleic acid and/or the linoleic acid derivative and
between 5 and 30 % by weight phospholipid.

23. The composition according to claim 22, wherein said composition contains water as solvent and wherein said composition has been filled in air-tight ampoules.

24. The composition according to one of the preceding claims wherein said composition comprises a first component and a separately packed second component, whereby said first component contains

a solvent,

at least one electrolyte and/or

water,

and said second component contains

said carrier material,

said linoleic acid and/or said linoleic acid derivative and

solvent, if necessary.

25. The composition according to claims 24, wherein one of the two components, preferably said first component, also includes a pH regulator.

26. The composition according to claims 24 or 25, wherein said second component is made up of linoleic acid and/or at least one linoleic acid derivative, whereby said linoleic acid or said linoleic acid derivative is chemically and/or physically bonded to said phospholipid carrier material.

27. The composition according to one of claims 24 to 26, wherein said first and/or said second component also contain usual additives.

28. The composition according to one of claims 24 to 26, wherein said first component contains

50 % by weight to 80 % by weight water and

0 % by weight to 20 % by weight solvent

and said second component contains

3 % by weight to 15 % by weight of said phospholipid carrier material acylated with said linoleic acid or with said linoleic acid derivative and

0 % by weight to 15 % by weight solvent.

29. The composition according to claim 28, wherein said water in said first component takes the form of an aqueous physiological saline solution.

30. The composition according to one of the preceding claims, wherein said composition comprises a further active ingredient

selected from the group consisting of erythromycin, an erythromycin salt, an erythromycin-derivative, tetracycline, azelaic acid and/or retinoic acid.

31. The use of the composition according to one of the preceding claims for the prophylaxis and/or therapy of acne and/or accompanying disorders related with acne.

32. The use of the composition according to one of the claims 1 to 29 for the prophylaxis and/or therapy of unclean or acnegenic skin.

Figure 1

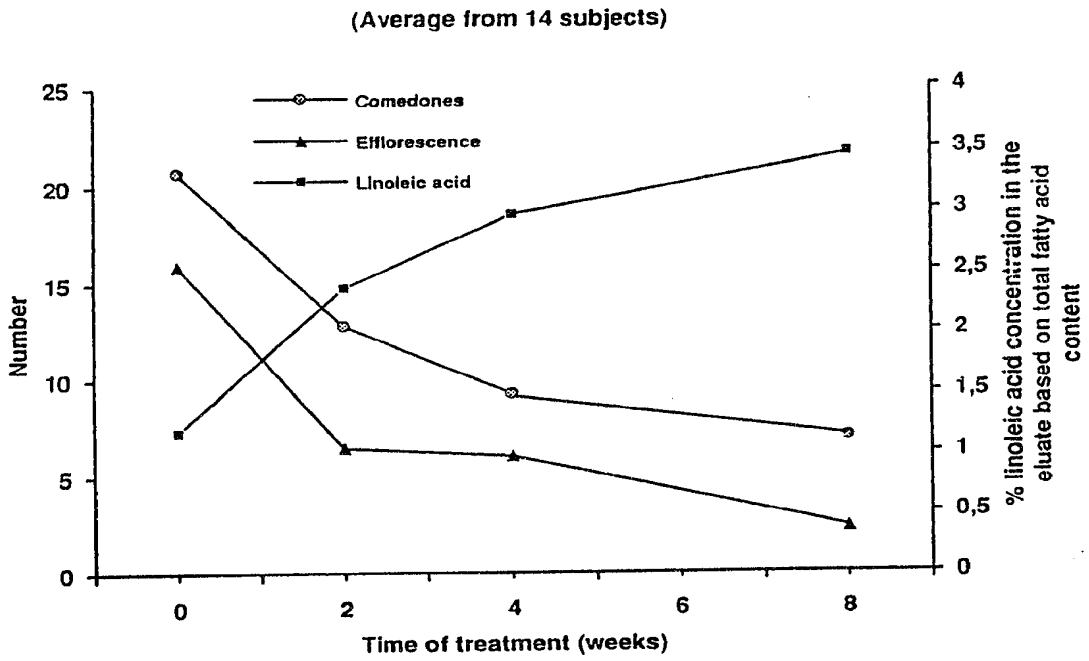
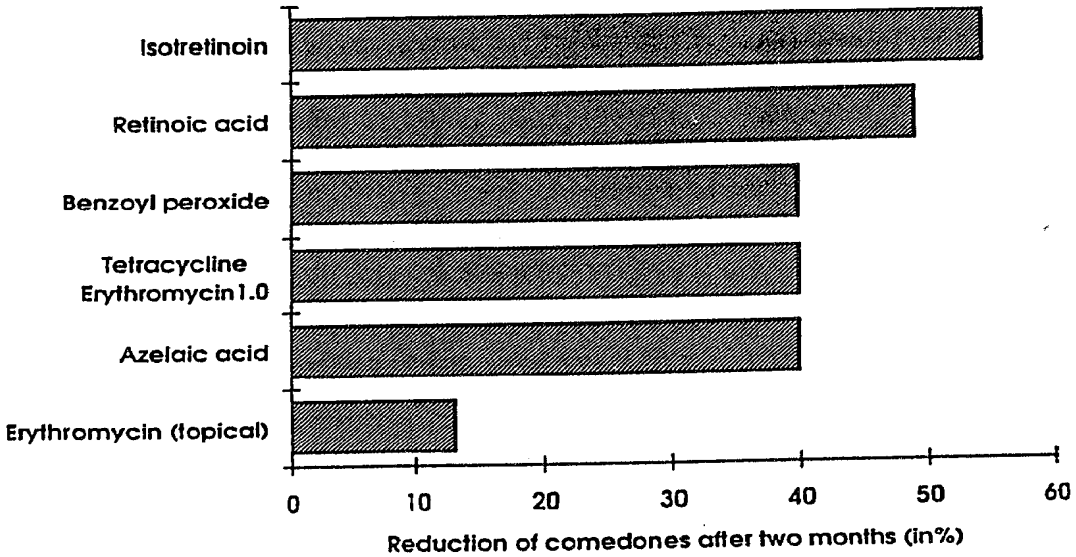

(Average from 14 subjects)
Comedones
Efflorescence
Linoleic acid
Number
% linoleic acid concentration in the eluate based on total fatty acid content
Time of treatment (weeks)
0
2
4
6
8
0
5
10
15
20
25
0
0,5
1
1,5
2
2,5
3
3,5
4

Figure 2


Isotretinoin
Retinoic acid
Benzoyl peroxide
Tetracycline
Erythromycin1.0
Azelaic acid
Erythromycin (topical)
0
10
20
30
40
50
60
Reduction of comedones after two months (in%)